Internal Lewis Acid Assisted Single Hydrogen Bond Donor Catalysis

A Senior Honors Thesis

Presented in Partial Fulfillment of the Requirements for graduation with *research distinction in Chemistry* in the undergraduate colleges of The Ohio State University

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A. Abstract.

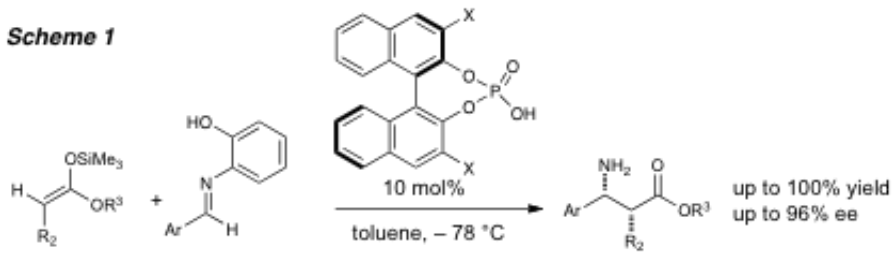
2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid has been identified as a new single hydrogen bond donor organic catalyst for the addition of indole to β-nitrostyrene. This catalyst offers enhanced reactivity over other benzoic acid derivatives lacking the boron substituent and it was reasoned this benefit results from the internal coordination the Lewis acid to the carboxylic acid functionality causing an increase in the acidity and improvement in catalyst function. Key features of 2-boryl benzoic acid catalysts making them particularly attractive include: their ease of preparation, shelf stability and convenience of use.

B. Background.

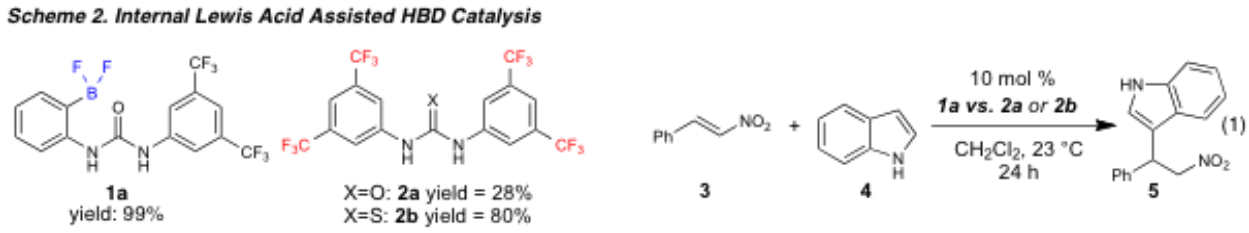
I. Catalysis. Chemical catalysis is a powerful tool in the field of organic synthesis. Advances in the area of catalysis directly benefit society in a number of ways, including improvements in the production of drugs and in the preparation of fine chemicals. A majority of the recent discoveries in chemical catalysis have taken advantage of the reactivity properties of transition metals. Only in the past ten years has the potential of catalyzing reactions with small organic molecules started to be uncovered. In addition to offering complementary reactivity patterns to transition metals, organic catalysts are relatively inexpensive and non-toxic.

II. Catalysis through Non-Covalent Interactions. Reactions catalyzed through non-covalent interactions are emerging as useful tools in organic synthesis for the preparation of valuable chiral molecules. Hydrogen bond donors (HBDs) are a particularly promising family of small molecules able to catalyze a number of interesting transformations.[1-4] Attractive features of HBDs include their stability, ease of preparation, low toxicity and potential to catalyze novel transformations. HBDs participating in the donation of a single hydrogen bond, as opposed to

those HBDs operating through dual hydrogen bonding, have recently become useful catalysts for a number of interesting transformations.



III. Single Hydrogen Bond Donor Catalysis. Phosphoric acids have emerged as valuable single HBD catalysts for the activation of imines.[4] Seminal work from Akiyama and coworkers demonstrated excellent yielding, highly selective additions of silyl enol ethers to imines in the presence of a suitable, chiral phosphoric acid (Scheme 1).[5] Over the past five years a number of advances made by several scientists have demonstrated phosphoric acids carry a great deal of potential and continued discoveries in the area are likely.[6-13]



IV. Internal Lewis Acid Assisted Hydrogen Bond Donors. In the past ten years ureas and thioureas have received a great deal of attention for their ability to operate as dual HBD catalysts. A recent advance in this area demonstrated the installation of a strategically placed internal Lewis acid is one strategy to enhance the reactivity of urea catalysts in the addition of indole to β-nitrostyrene through proposed increased polarization of the urea functionality (Scheme 2, eq 1). The promising nature of this activation strategy in dual HBD catalysis led us

to reason appropriate single hydrogen bond donor catalysts could also benefit from internal Lewis acid assisted activation and so we set out to investigate 2-silyl benzoic acid (**6**) and 2-boryl benzoic acid (**7**) derivatives as novel single hydrogen bond donor catalysts (Figure 1). Indeed, prior to our investigations these conceptually interesting classes of catalysts had gone unexplored.

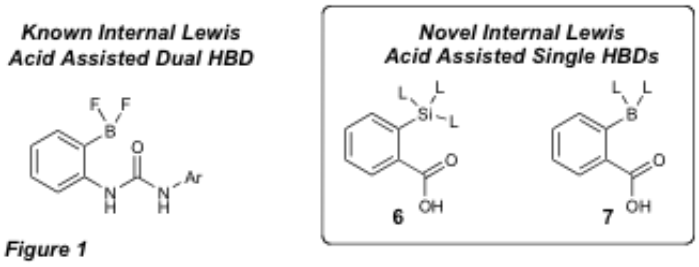
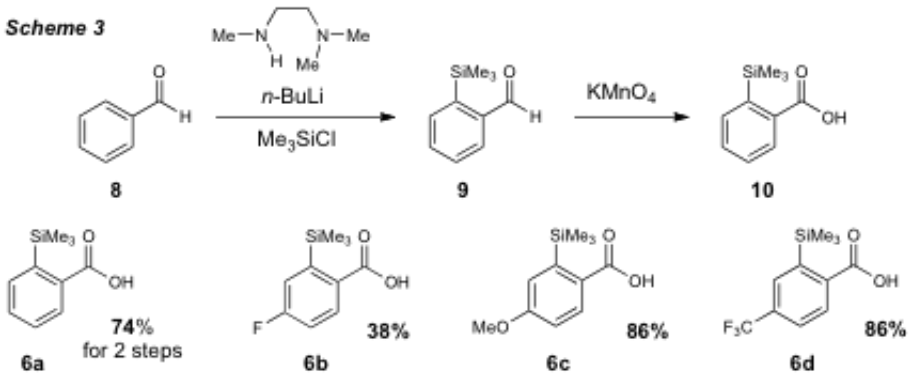


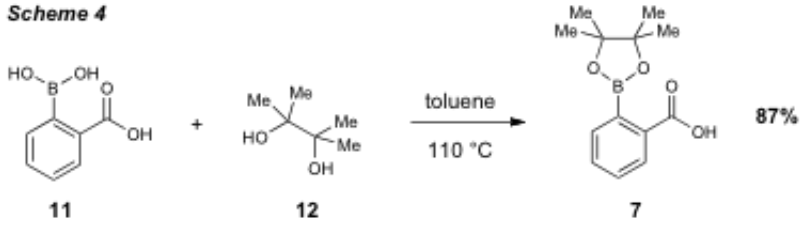
Figure 1

C. Results

I. 2-Silyl Benzoic Acid Synthesis. The synthesis of the 2-silyl benzoic acids (**6**) began with *ortho*-lithiation of the appropriate benzaldehyde derivative (**8**) using *n*-butyl lithium in the presence of N^1,N^1,N^2-trimethylethane-1,2-diamine followed by the addition of trimethylsilyl chorlide to give rise to the *ortho*-silyl benzaldehyde derivative **9** (Scheme 3). Oxidation to the carboxylic acid was achieved in good yield under standard conditions using potassium permanganate. Four 2-silyl benzoic acid derivatives (**6a**-**6d**) containing both electron donating and withdrawing groups were prepared in good yield (38-86% over two steps) using this method. All of the silyl benzoic acid catalysts prepared were white solids that could be easily stored on the bench with no observed decomposition over a period of several months.



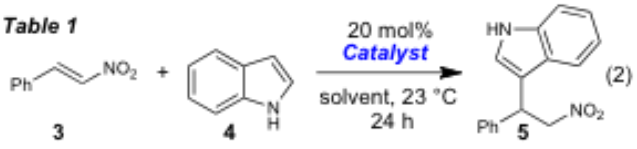
II. 2-Boryl Benzoic Acid Synthesis. 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid was prepared in just one step from commercially available materials (Scheme 4). Condensation of pinacol (**12**) with boronic acid **11** under Dean-Stark conditions generated **7** in 87% yield. Similar to the silyl benzoic acids prepared, the boryl benzoic acid **7** was isolated as a bench stable white solid that was convenient to work with.



II. Catalyst Structure Survey. With the desired internally activated benzoic acid derivatives in hand, attention was turned toward evaluating their potential as catalysts in the addition of indole to β-nitrostyrene (Table 1). Our initial attempt with benzaldehyde-derived benzoic acid derivated **6a** was rather unsuccessful affording just 10% of the desired adduct **5** (entry 1). We hypothesized the internal Lewis acid working in conjunction with an electron-withdrawing group may lead to enhanced activity. Gratifyingly, 10 mol % of catalyst **6d** afforded a dramatic improvement giving rise to 76% of **5** after 24 h in toluene (entry 2). Further probing of the catalyst structure led us to conclude the reactivity of the 2-silyl benzoic acid catalysts was easily

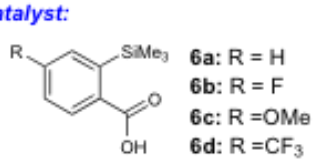
altered by the substituents on the aromatic ring. A *p*-fluoro substituted catalyst **6b** generated a moderate yield of **5** (43%, entry 4). Not surprisingly, catalyst **6c**, derived from *p*-anisaldehyde, provided little catalysis yielding just 14% of **5** (entry 5). While we were pleased with the results of catalyst **6d**, there were concerns the majority of the improved activity was originating from the electron-withdrawing group and little internal Lewis acid assistance was playing a role because catalyst **6a** operated so inefficiently (entry 1 vs. entry 2). It was reasoned better results might be achieved through the installation of a stronger Lewis acid, such as boron. Indeed we found this to be the case when subjection of **3** and **4** to 10 mol % of **7** gave rise to 94% of **5** after 24 h in methylene chloride (entry 7). Control experiments carried out with catalysts **11** and **12** provide some evidence surrounding the properties of the catalysts. Internal Lewis acid coordination does seem to be playing a role in the reactivity of the catalyst as catalyst **11** provides just 16% of **5** after 24 h (entry 6). Treatment of **3** and **4** to 10 mol % of methyl ester **12** affords just 17% of **5** under otherwise identical reaction conditions (entry 8). This suggests the carboxylic acid functionality is critical to the reactivity of the catalyst; we propose it is operating through hydrogen bonding interactions.

Table 1

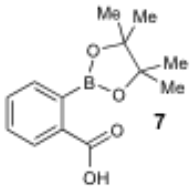


entry	solvent	catalyst	yield (%)
1	$PhCH_3$	**6a**	10
2	$PhCH_3$	**6d**	76
3	CH_2Cl_2	**6d**	59
4	$PhCH_3$	**6b**	42
5	$PhCH_3$	**6c**	14
6	$PhCH_3$	**11**	16
7	CH_2Cl_2	**7**	94
8	CH_2Cl_2	**12**	17

Catalyst:



6a: R = H
6b: R = F
6c: R =OMe
6d: R =CF_3



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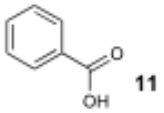

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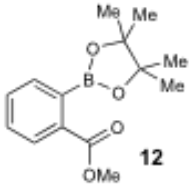

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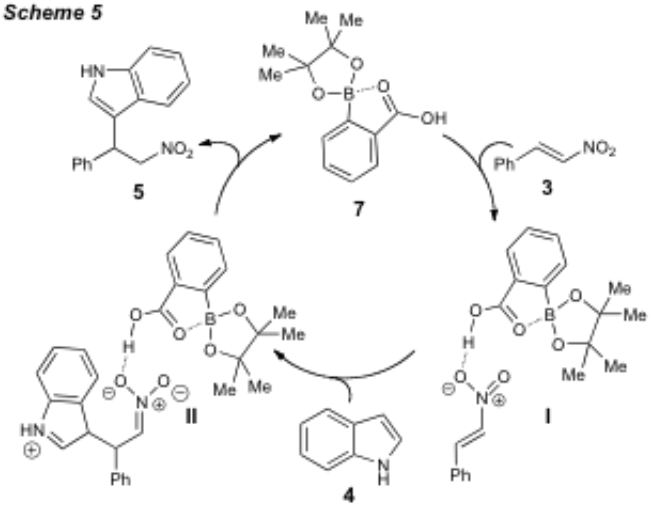
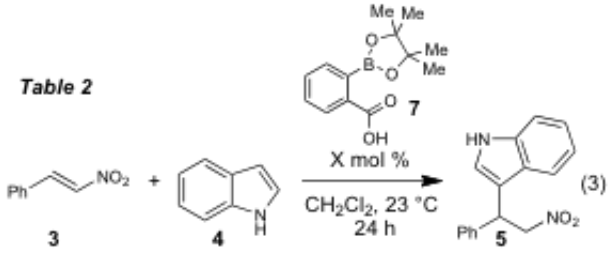
A proposed catalytic pathway is depicted in Scheme 5. Coordination of catalyst **5** with the nitrosytrene generates **I**, a species activated for nucleophilic attack. At this time the indole undergoes conjugated addition to **I** giving rise to **II**. After proton transfer product 5 is formed and with simultaneous reintroduction of catalyst **7** into the cycle.

Scheme 5



II. Catalyst Loading Study. Once the structure of the catalyst had been optimized, the limits of the reaction with respect to 2-boryl benzoic acid **7** loading were explored (Table 2). The reaction was carried out under the previously optimized reaction conditions varying concentration of the catalyst from 20 mol % down to 2.5 mol %.

Table 2



entry	mol % **7**	yield (%)
1	20	94
2	10	75
3	5	40
4	2.5	39

Reactions carried out with 20 mol % of **7** afforded a 94% yield of **5** after 24 h in methylene chloride (entry 1). Reducing the catalyst loading to 10 mol % still generated a high

yield of **5** after 24 h (75%, entry 2). Catalyst loadings of 5 mol % and 2.5 mol % gave rise to moderate yields of product (entries 3 and 4) after 24 h; however it is speculated that longer reaction times would likely improve reaction conversion and lead to excellent yields of **5**.

D. Future Directions

Now that 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (**7**) has been developed as a highly effective catalyst for the addition of indole to β-nitrostyrene, efforts should next be directed toward further refining the catalyst structure and evaluating the generality of the reaction in the context of both the electrophile and nucleophile. Studies should first focus on the electronic nature of the catalyst. Specifically, the effect of electron-donating and -withdrawing groups on this catalyst should be examined. Once the optimal structure of the 2-boryl benzoic acid is identified and the catalyst loading has been tested, the direction of the project should turn to an examination of the reaction scope. This should be achieved through study of how well the reaction tolerates electron-donating and withdrawing groups on the nitrostyrene. Nitroalkenes derived from alkyl aldehydes will also be studied to fully explore the potential of this new catalyst. Investigations regarding the reactions ability to accommodate substituted indoles and other nitrogen heterocycles, such as pyrroles, will also be key in determining the generality, and ultimately the utility, of internal Lewis acid assisted single HBD catalysis in this chemical transformation.

E. Conclusions

The internal activation of benzoic acid with an *ortho* boron pinacol ester substituent generates a small organic molecule that operates well as a single hydrogen bond donor catalyst for the addition of indole to β-nitrostyrene. This new organic catalyst has several attractive

features, such as: it is easy to prepare, stable and convenient to use. Continued investigations of internal Lewis acid assisted single hydrogen bond donors may lead the development of a new class of organic catalysts with applications in unique reactivity patterns.

F. Experimental Procedures

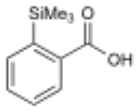
General Methods. Methylene chloride and toluene were freshly distilled from CaH_2 prior to use. Purification of reaction products was carried out by flash chromatography using Sorbent Technologies 60 Å (40 - 63 μm). Analytical thin layer chromatography was performed on EMD Chemicals 0.25 mm silica gel 60-F_{254} plates. Visualization was accomplished with UV light and potassium permanganate or ceric ammonium molybdate stains followed by heating. Melting points (**mp**) were obtained on a Thermo Scientific Mel-temp apparatus and are uncorrected. Infrared spectra (**IR**) were obtained on a Perkin Elmer Spectrum 100R spectrophotometer. Infrared spectra for liquid products were obtained as a thin film on a NaCl disk, and spectra for solid products were collected by preparing a NaBr pellet containing the title compound. Proton nuclear magnetic resonances (**^{1}H NMR**) were recorded in deuterated solvents on a Bruker Avance DPX 400 (400 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm, d) using the solvent as internal standard ($CHCl_3$, d 7.27 and DMSO, d 2.50) ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), or quartet (q). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m) or broad (br). Coupling constants are reported in Hertz (Hz). Proton-decoupled carbon (**^{13}C-NMR**) spectra were recorded on a Bruker Avance DPX 400 (100 MHz) spectrometer and are reported in ppm using the solvent as an internal standard ($CHCl_3$, d 77.0; DMSO, d 39.5). Electrospray mass spectra (**ESI-MS**) were obtained using a Bruker MicrOTOF Mass Spectrometer. Gas Chromatography (**GC**) analysis data were obtained on Agilent 6850 Series GC System with a

7673 Series Injector. An HP-1 capillary 30 m column was employed (19091Z-413E). Unless otherwise noted, all other commercially available reagents and solvents were purchased from Aldrich and used without further purification. HPLC analyses were obtained on a Perkin Elmer Series 200 HPLC with multiple wavelength detector.

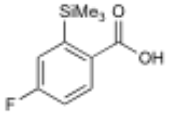
General Procedure for the Preparation of 2-Silyl Benzoic Acid Derivatives: N^1,N^1,N^2-trimethylethane-1,2-diamine (1.2 equiv) is added to THF (15.0 mL) at -20 ºC. *n*-Butyl lithium (1.03 equiv) are added to the solution dropwise and the resulting solution is stirred for 15 min giving rise to a dark red solution. Freshly distilled benzaldehyde (1 equiv) is added to the solution and stirring is continued for an additional 15 min. *n*-Butyl lithium (3.10 equiv) is added and the resulting dark red solution and is put in the freezer at 4 °C for 24 h. At this time, the reaction mixture is removed from the freezer and cooled to -42 °C with magnetic stirring. Freshly distilled trimethylsilyl chloride (6.0 equiv) is then added and the solution stirred at -42 ºC for 30 min and then stirred for another 30 min at 23 °C. The solution is poured into 10% HCl (40 mL) and extracted with ether (3x40 mL). The organic extract is washed with saturated NaCl (40 mL). The solution is then dried with $MgSO_4$, filtered and concentrated to afford a clear, colorless liquid that is purified over by flash column chromatography on silica gel.

The aldehyde (3.59 mmoles) isolated above is then measured into a 35 mL rb flask and acetone (9.8 mL) and water (1.57 mL) are added to the flask and the resulting solution is cooled to 0 °C. $KMnO_4$ (1.2 eq) is then carefully added to the reaction small portions to generate a deep purple solution that is stirred for 5 min at 0 °C then warmed to 23 °C and stirred for 1.5 h. Upon confirmation the reaction is complete by TLC analysis, the solvent is evaporated and the resulting oil is dissolved in saturated sodium sulfite (30 mL). The solution is then filtered through a pad of Celite 545, and the solid is washed with water (3x10 mL) and with DCM (3x10

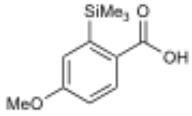
mL). The filtrate is acidified with 10% HCl, and extracted with DCM (3x30 mL). The organic extracts are dried with sodium sulfate and then evaporated. The white solid is then dried on the vacuum pump.



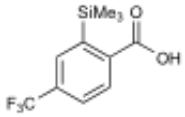
2-(trimethylsilyl)benzoic acid (6a): Obtained as a white solid (74%). R_f = 0.73 (2:3 ethyl acetate:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) d8.19-8.17 (m, 1H); 7.75-7.73 (m, 1H); 7.592-7.460 (m, 2H); 0.415 (s, 9H).



4-fluoro-2-(trimethylsilyl) Obtained as a white solid (38%). R_f = 0.56 (2:3 ethyl acetate:hexanes)

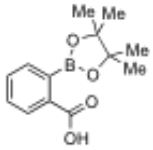


4-methoxyl-2-(trimethylsilyl)benzoic acid (6c): Obtained as a white solid (86%). R_f = 0.64 (2:3 ethyl acetate:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) d8.22-8.20 (m, 1H); 7.26-7.25 (m, 1H); 6.96-6.93 (m, 1H); 0.372 (s, 9H)



4-trifluoromethyl-2-(trimethylsilyl)benzoic acid (6d): Obtained as a white solid (86%). R_f = 0.38 (2:3 ethyl acetate:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) d8.29-8.27 (m, 1H); 7.98 (s, 1H); 7.76-7.74 (m, 1H); 0.372 (s, 9H)

Procedure for the Preparation of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid:



2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (7): 2-carboxybenzene boronic acid (3.0 mmol) and toluene (5 mL) are added a flame dried 15 mL round-bottomed flask equipped with a Dean-Stark trap and reflux condenser and put under nitrogen atmosphere. 2,3-dimethylbutane-2,3-diol (3.0 mmol) is added to the reaction flask and the mixture is refluxed for 24 h at 110 ºC. The white solid generated

over the course of the reaction is collected by vacuum filtration and washed with the toluene from the Dean-Stark trap. The solid is then dried on the vacuum pump. Obtained as a white solid (87%). R_f = 0 (2:3 ethyl acetate:hexanes); ^{1}H NMR (400 MHz, DMSO) d7.39-7.37 (m, 1H); 7.32-7.25 (m, 2H) 1.09 (s, 12H)

General Procedure for the Addition of Indole to β-Nitrostyrene: The trans-β-nitrostyrene solid (28.0 mg, 0.188 mmoles) and the respective catalyst (0.0367 mmoles) under study are measured and added to a dram vial. The dram vial is put under argon atmosphere. The indole is measured and added to the same dram vial. The solvent (156 μL) is then added to the reaction mixture and then trifluoroethanol of one equivalent (13 μL) is added to the reaction mixture. The reaction is allowed to run for 24 h. The crude reaction is purified through 25 g of silica gel to afford a pale yellow-orange oil. The reaction is run with a theoretical yield of 50 mg.

References.

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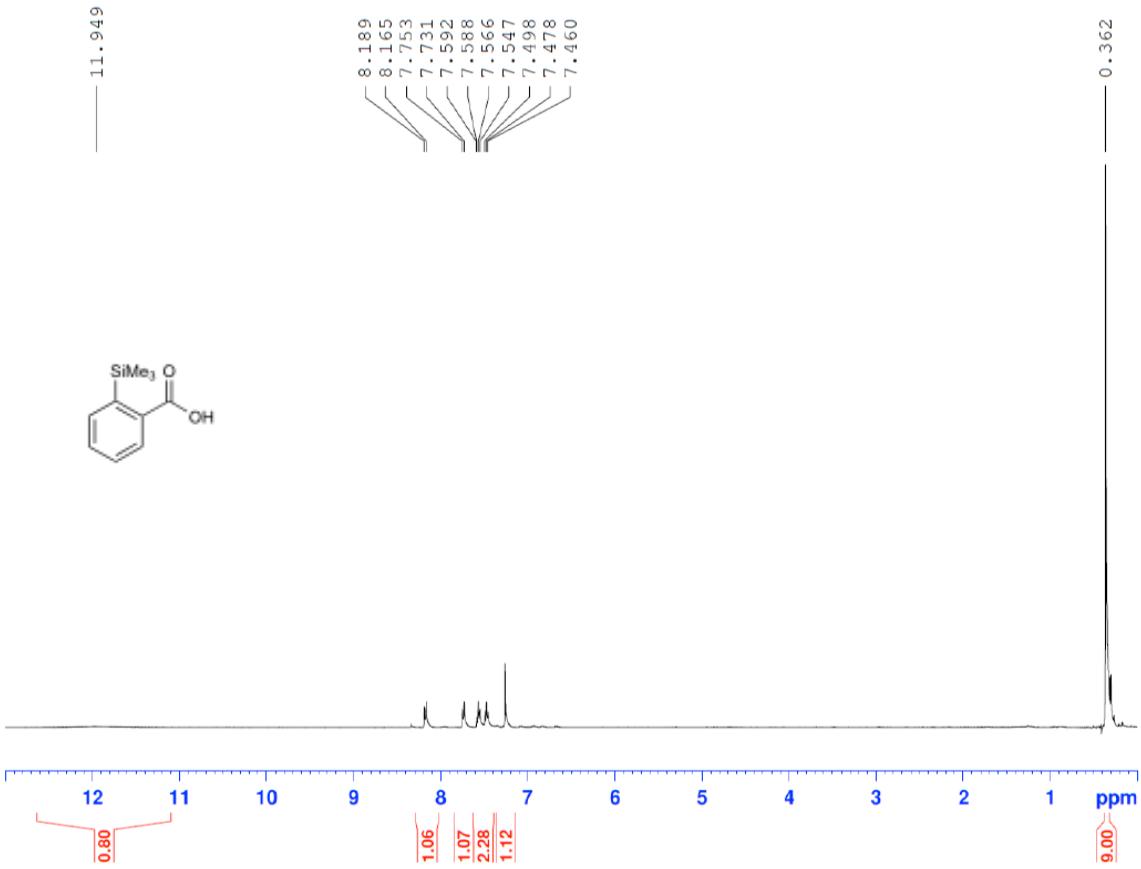
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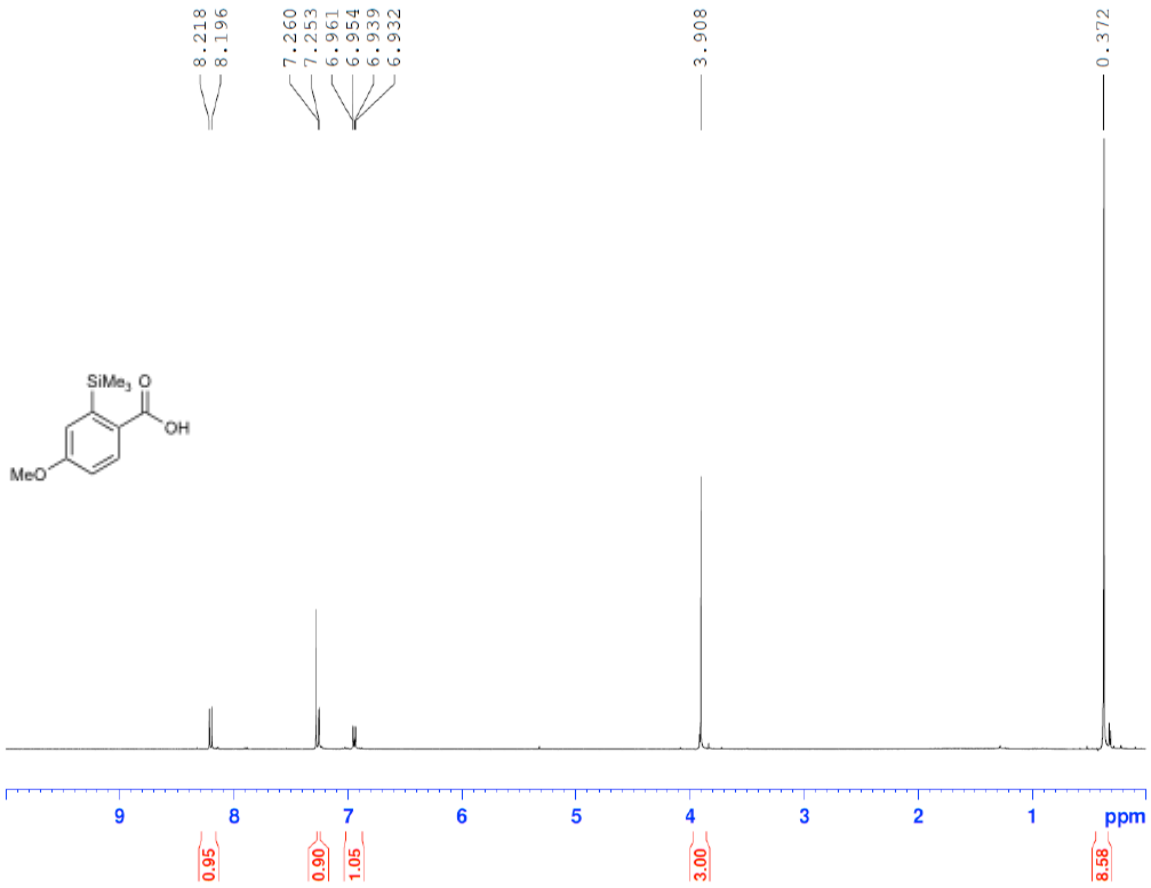
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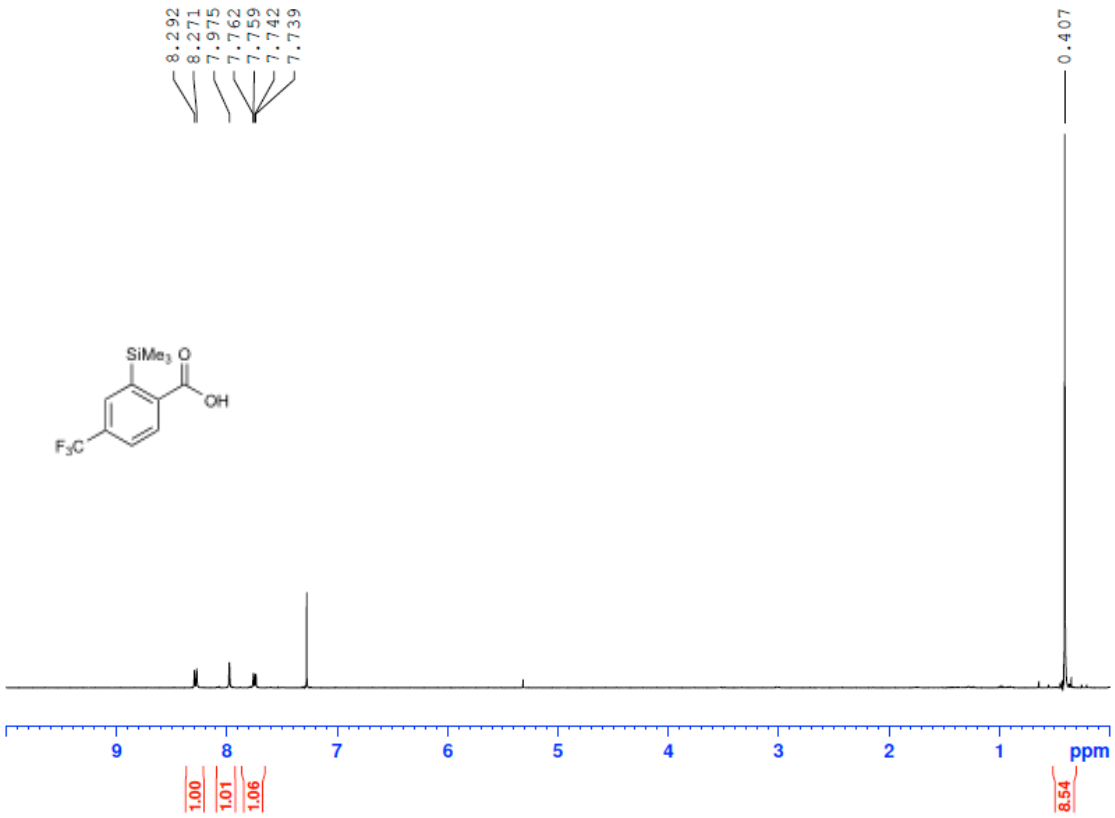
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7.762
7.759
7.742
7.739
0.407
SiMe3
O
OH
F3C
9
8
7
6
5
4
3
2
1
ppm
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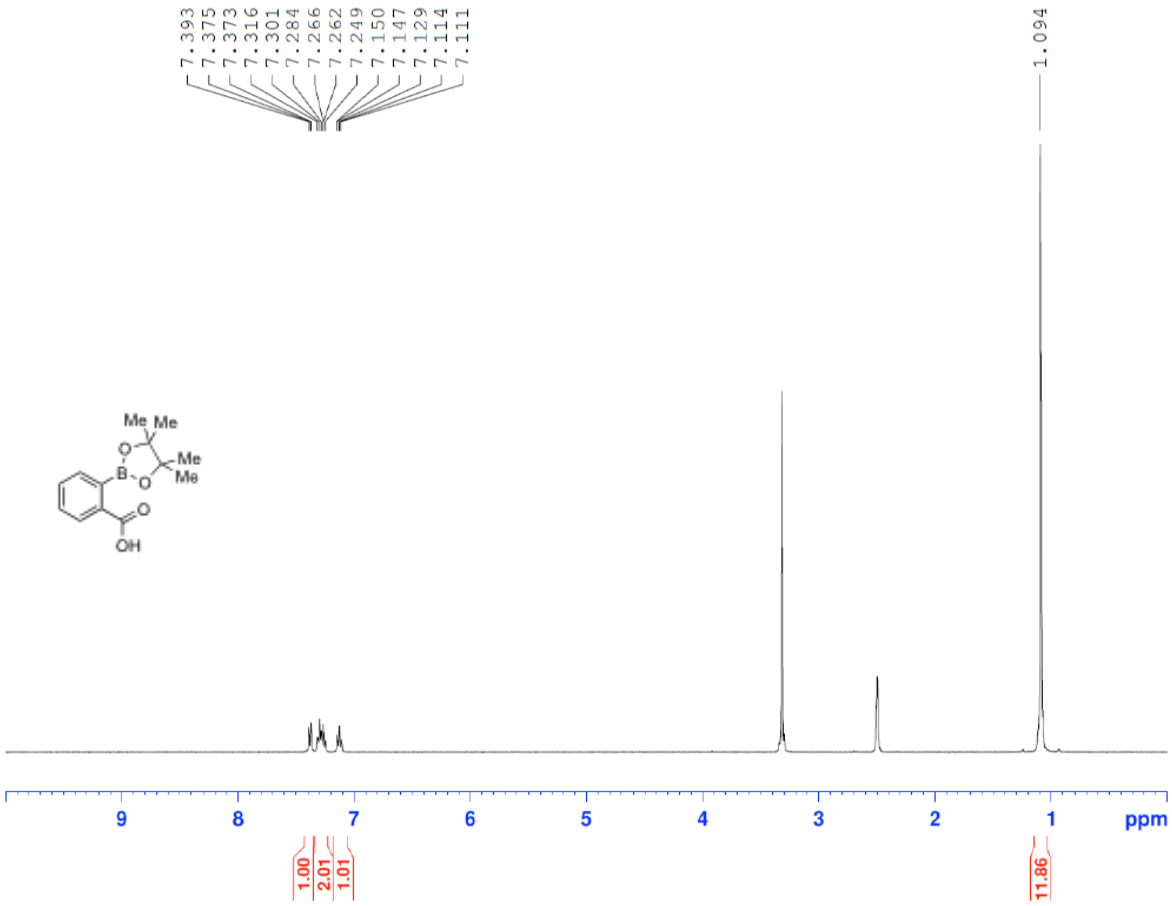
1.01
1.06
8.54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7.373
7.316
7.301
7.284
7.266
7.262
7.249
7.150
7.147
7.129
7.114
7.111
1.094
Me
Me
Me
Me
O
B
O
O
OH
9
8
7
6
5
4
3
2
1
ppm
1.00
2.01
1.01
11.86